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VERIFICATION OF A TRANSLATION

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Director to RWS Group plc, of Europa House, Marsham Way, Gerrards Cross, Buckinghamshire, England declare:

That the translator responsible for the attached translation is knowledgeable in the German language in which the below identified international application was filed, and that, to the best of RWS Group plc knowledge and belief, the English translation of the international application No. PCT/EP00/08538 is a true and complete translation of the above identified international application as filed.

I hereby declare that all the statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the patent application issued thereon.

Date: 28 February 2002

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Low-viscosity, hot water-coagulable cellulose ethers, process for the preparation thereof by depolymerization, and the use thereof

- 5 The present invention relates to low-viscosity, hot water-coagulable cellulose ethers of high purity and high whiteness, to a process for the preparation of these cellulose ethers by depolymerization by means of acid-catalyzed, hydrolytic degradation, where appropriate in the presence of an oxidizing agent, and to the use thereof.
- 10 The degradation of cellulose ethers with high degrees of polymerization has been known for a long time and can be achieved in diverse ways. In particular, degradation to very low-viscosity products has attracted great attention since these products can be employed advantageously inter alia as coating material for
- 15 active pharmaceutical ingredients or seeds, but also, for example, in suspension polymerization. Cellulose ethers whose Höppler viscosity, measured as 2.0% solution (absolutely dry) in water at 20°C, is not more than 50 mPas are referred to hereinafter as very low-viscosity products.
- 20 The processes employed for degrading cellulose ethers include, besides acid-catalyzed hydrolytic cleavage of the acetal linkage, inter alia oxidative degradation and degradation by high-energy radiation or microorganisms/enzymes.
- The reduction in the viscosity of cellulose ethers by irradiation with high-energy
- 25 radiation is described, for example, in DE-A-44 34 280 and US-A-2 895 891. Salt-free cellulose ethers are also crosslinked instead of degraded if suitable reaction conditions are chosen. The disadvantages of the process are essentially the production of inhomogeneous materials (dependence of the degree of polymerization on the layer thickness irradiated, depth of penetration of the
- 30 radiation, radiation intensity), the impossibility of removing by-products of the reaction from the mixture, and the radiation treatment which is generally exposed to public criticism.

Processes for the oxidative degradation of cellulose ethers are described inter alia in US-A-2 912 431, US-A-4 316 982, CH-B-461 455, DE-A-20 16 203 and GB-B-953 944.

- 5 US-A-2 912 431 describes a process in which hypohalites, peroxides or periodates degrade carboxymethylcelluloses in a mixture with aqueous alcohol at 40 to 80°C with simultaneous bleaching.

The degradation of cellulose ethers which are moist with water and have a dry content of 40 to 75% using ozone/air/oxygen mixtures at 0 to 60°C is described in

- 10 US-A-4 316 982. CH-B-461 455 describes a process in which the cellulose ether with a maximum water content of 75% is mixed with 0.1 to 10% strength aqueous hydrogen peroxide solution. The resulting mixture is then oxidatively degraded and dried at 100 to 250°C until the H_2O_2 is consumed.

DE-A-20 16 203 describes a process for the degradation of cellulose ethers in

- 15 which a very substantially dry powder with a maximum water content of 5% is mixed with a hydrogen peroxide solution and degraded at 50 to 150°C.

In GB-B-953 944, the viscosity of water-soluble, nonionic cellulose ethers is reduced in the dry or moistened state by reaction with H_2O_2 at elevated temperatures.

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The oxidative degradation of cellulose ethers usually leads to the formation of numerous by-products.

If the degradation takes place on the moist or finished product without a subsequent purification step in order to optimize the yield, the by-products which

- 25 have formed are no longer removed from the depolymerized product. Very low-viscosity cellulose ethers prepared by oxidative degradation are normally colored because of the drastic reaction conditions.

Simple hydrolytic degradation processes with inorganic or organic acids are described, for example, in US-A-1 679 943, US-A-1 943 461, EP-B-0 497 985 and

- 30 EP-A-0 210 917.

In US-A-1 943 461, the preground cellulose ethers are degraded with dilute acids or mixtures thereof (concentration 0.5 to 5%, a multiple of the weight of the cellulose ether to be degraded) in a closed pressure vessel under a pressure of

0.7 to 5.2 bar and at temperatures of from 115 to 160°C for 20 to 60 minutes. US-A-1 679 943 describes the degradation of cellulose ethers with various acid mixtures without either a pressure vessel or an elevated temperature being required. However, especially at room temperature, this results in unacceptably
5 long reaction times, which may be in the region of several days.

In EP-B-0 497 985, pulps with a low copper number, i.e. high α -cellulose content, are washed, dried, ground and mixed with a 0.5% by weight aqueous HCl solution at a temperature of about 70°C. The water content of the cellulose ether plays an
10 important part in this process. On the one hand, it must not fall below 1% during drying because excessive drying leads to hornification and yellowing of the products but, on the other hand, it must not be more than 5% during the degradation because considerable amounts of water favor gel formation with low molecular weight cellulose ethers. The resulting cellulose ethers have very low
15 viscosities (< 20 mPas, 2.0% solution at 20°C). A similar process is described in EP-A-0 210 917. In this case, a cellulose ether powder containing 3 to 8% water is degraded with 0.1 to 1% by weight of an aqueous HCl solution at 40 to 85°C.

Degradation in particular to very low-viscosity products of high purity cannot be
20 achieved by using HCl as gas. Processes of this type are described, for example, in US-A-3 391 135 and US-A-4 061 859.

US-A-3 391 135 discloses a process for preparing cellulose ethers with solution viscosities of less than 10 mPas (2.0% solution at 20°C) from high-viscosity
25 cellulose ether powders with water contents of less than 5% at 30 to 80°C. Excess HCl gas is removed and the cellulose ether is then neutralized by admixing a weak base.

According to US-A-4 061 859, cellulose ethers are degraded as dry powders with a water content of from 0.01 to 5% by weight using hydrogen halide at 15 to 80°C,
30 and then neutralized by mixing sodium bicarbonate or passing in ammonia gas. Bleaching of the material obtained is achieved with sulfur dioxide gas, with which the degraded material is brought into contact after the depolymerization stage. It is possible with this process to degrade cellulose ethers to very low-viscosity

products whose initial viscosity was several hundred thousand mPas. The bleaching stage following the depolymerization makes it possible to brighten the products.

- 5 Hydrolytic degradation is mild and neutral in relation to functional groups and can be employed for preparing very low-viscosity products. However, if the cellulose ether to be degraded is present in relatively great dilution in aqueous medium, it is scarcely possible to avoid losses of yields through partial developing of the material. If, on the other hand, completely worked up, ground and dried cellulose
- 10 ethers are degraded with a little aqueous or gaseous HCl, neutralization by admixture with weak bases is necessary. This increases the salt content of the finished product and by-products of the reaction are not removed from the product. If the water content during the degradation is too high it is possible only with difficulty to avoid partial dissolving and adhesion of the material.
- 15 Homogeneous distribution of the small amounts of acid and a maximally uniform degree of polymerization are then likewise difficult to achieve. If the reaction is carried out under particularly mild conditions it is possible only to reduce but not suppress yellowing. Although subsequent bleaching of the products increases the whiteness of the material, it means an additional process step and does not lead
- 20 to removal of the by-products formed.

It was therefore an object of the present invention to provide a process for the depolymerization of cellulose ethers which does not have the prior art disadvantages mentioned.

- 25 In particular, possible ways were sought for preparing very low-viscosity cellulose ethers which, besides maximally uniform degrees of polymerization and small by-product constituents, have a very low salt content and a high whiteness and are intended to provide clear solutions with high transmittances so that they can advantageously be employed in particular in the sectors of drugs coating (tablets,
- 30 coated tablets, capsules), cosmetics, foodstuffs and suspension polymerization.

This object is achieved by a process for the depolymerization of hot water-coagulable cellulose ethers by hydrolytic degradation by means of acids, which is

characterized in that the degradation is carried out at a temperature above the cloud point of the cellulose ether as concentrated aqueous slurry.

It is possible in this connection to use as cellulose ethers all cellulose ethers
5 known to be hot water-coagulable.

Preference is given to alkylcelluloses such as, for example, methyl-, ethyl- and propylcellulose, and mixed ethers thereof, such as for example, hydroxyethylmethyl-, hydroxypropylmethyl-, ethylhydroxyethyl- and
10 ethylmethylcellulose.

The preparation and working up of the cellulose ethers employed for the degradation is not restricted in any way at all. They can be prepared and worked up by all processes known to the skilled worker (Ullmann's Enzyklopädie der
15 Technischen Chemie; Volume 9, "Celluloseether", Verlag Chemie, Weinheim, 4th edition 1975, pp. 192 ff).

The degree of polymerization and the viscosity of the cellulose ethers to be employed is likewise not restricted in any way at all. However, the cellulose ether
20 employed for the degradation ought preferably to have a degree of polymerization not too far removed from the degree of polymerization which is intended to be achieved by the depolymerization.

In a particularly preferred embodiment, the process of the invention is used to
25 prepare very low-viscosity cellulose ethers which have Höppler viscosities measured as 2.0% solution (absolutely dry) in water at 20°C of ≤ 50 mPas.

Acids suitable for the hydrolytic degradation are mineral acids, but also strong organic acids, and mixtures thereof. However, mineral acids are preferred.
30

The mineral acids particularly preferably employed are hydrochloric acid, sulfuric acid, nitric acid and phosphoric acid. However, it is also possible to use mixtures thereof.

Strong organic acids employed are preferably trifluoroacetic acid, acetic acid, formic acid, oxalic acid, phthalic acid, maleic acid and benzoic acid. However, it is also possible to use mixtures thereof.

- 5 The acid-catalyzed hydrolytic degradation is carried out according to the invention above the cloud point of the cellulose ether. A temperature range from 70 to 105°C is preferred.

- 10 The process of the invention is additionally characterized in that degradation is carried out as concentrated slurry. The ratio of water to cellulose ether preferably does not exceed 10:1, particularly preferably does not exceed 7:1 and in particular does not exceed 5:1, by weight. The use of minimal amounts of water as suspending agent leads to very small losses of yield, which are generally caused by the dissolving of low-viscosity constituents.

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In a further preferred embodiment, in addition oxidizing agents are added to the concentrated aqueous slurry before, during and/or after the depolymerization in acidic or neutral medium.

- 20 The oxidizing agents preferably employed are hydrogen peroxide and salts thereof, other peroxy compounds such as for example, sodium peroxosulfate, perborates (also in combination with activators such as TAED), sodium chlorite, halogens, halogen oxides and other compounds employed for bleaching. Hydrogen peroxide (H₂O₂) is particularly preferred.

25

The oxidizing agents are generally employed in this connection in amounts of from 0.01 to 20% by weight, preferably 0.01 to 10% by weight and particularly preferably 0.01 to 5% by weight, based on the cellulose ether.

- 30 It has been found, surprisingly, that the addition of oxidizing agents even in small amounts of distinctly less than one percent, preferably during the hydrolytic degradation, in addition to reducing the viscosity leads to by-products of the reaction which are normally at least partly adsorbed onto the cellulose ether and

cause a coloration thereof being converted by oxidation into a form with better solubility in water. This leads to an improved removal of the by-products from the depolymerized cellulose ether. Consequently, the use of oxidizing agents such as, for example, H_2O_2 , leads to an improvement in the whiteness of the products with a simultaneous increase in the degree of uniformity. Moreover, the addition of oxidizing agents ensures an additional reduction in the final viscosity under conditions which are otherwise identical. It is thus possible to ensure a defined target viscosity to shorten the reaction time and/or reduce the amount of acid compared with carrying out the process without the addition of oxidizing agents.

10

Addition of the oxidizing agent is in principle also conceivable before or after the hydrolytic degradation by means of acids, but addition during the depolymerization is preferred.

15 The degradation and additional brightening through oxidation and/or removal of by-products can be carried out either in one step or else in succession, specifically both in the acidic medium and after (partial) neutralization has taken place.

A further possibility is to carry out the degradation both on the ready-formulated product and on moist crude products with the usual moisture content. Since a subsequent drying and grinding is necessary for formulating the product, it is preferred for moist crude products as result in production processes to be used for the degradation.

25 The degradation may, for example, be carried out in place of the last washing step when the salt content has been partly reduced, because excess salt from the reaction to give the cellulose ether is likewise removed by the aqueous slurry. The resulting products have an extremely low salt content.

30 The aqueous solutions of the degraded cellulose ethers usually have slightly acidic pH values due to the generation of acidic groups on the basic cellulose ether framework. The pH of these solutions can be adjusted to a substantially neutral pH of 5.5 to 8.0 by using, after the depolymerization, not water but an

aqueous solution of at least one basic salt (such as, for example, sodium carbonate, sodium bicarbonate, sodium sulfate, sodium bisulfate) to wash the degraded cellulose ether, at a temperature above the cloud point of the degraded cellulose ether, to wash out the by-products of the reaction. An additional mixing
5 step as described in other processes for adjusting a target pH is unnecessary. The base is uniformly distributed and the cellulose ether can in the normal process be dried and ground in one or more steps.

The yields of the described process are generally between about 80% and 96%,
10 depending on the required final viscosity and the level of the cloud point of the cellulose ether to be degraded. Since in the aqueous working up of cellulose ethers a washing loss between 3 and 8% usually occur, depending on the viscosity, and the degradation can be carried out in place of a washing step, the losses of yield are minimized. It is possible to increase the yield, in particular with
15 products having a high cloud point, by increasing the temperature of degradation when carried out in a pressure apparatus.

The viscosity of the resulting products can essentially be adjusted as desired via the amount of acid employed, the reaction time and, where appropriate, the amount of additional oxidizing agent, and is very reproducible. Because of the
20 uniform degradation associated with good mixing and distribution of the reactants, the products have virtually uniform degrees of polymerization.

It is possible to prepare by the process of the invention cellulose ethers with high purity and high whiteness. Particularly good results are achieved in the
25 preparation of methylhydroxypropylcelluloses.

The present invention thus further relates to methylhydroxypropylcelluloses with a Höppler viscosity measured on a 2.0% solution (absolutely dry) in water at 20°C preferably of ≤ 50 mPas and particularly preferably ≤ 5 mPas.

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The whiteness of the methylhydroxypropylcelluloses with a viscosity in the range from 5 to 50 mPas is preferably above 60% and of methylhydroxypropylcelluloses whose viscosity is ≤ 5 mPas is preferably above 50% (basis: DIN standard 5033).

Since the whiteness depends inter alia on the particle size distribution of the cellulose ether, the stated values relate to products whose proportion of particles with a size of $< 125 \mu\text{m}$ does not exceed 50%, but is preferably less than 10%.

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The salt content of the prepared cellulose ethers is preferably below 0.4% by weight, particularly preferably below 0.2% by weight and especially below 0.1% by weight.

- 10 Particularly preferred methylhydroxypropylcelluloses have a content of methoxy groups in the range from 28 to 32% by weight and a content of hydroxypropyl groups in the range from 5 to 9% by weight.

- 15 The described cellulose ethers are, because of their purity and high whiteness, especially suitable for coating pharmaceuticals and seeds and for use in cosmetics, foodstuffs or in suspension polymerization.

The invention is described in detail below by means of exemplary embodiments without, however, being restricted thereby.

20

The viscosities were measured in the examples, unless expressly noted otherwise, 2.0% strength (absolutely dry), in aqueous solution using a Höppler falling ball viscometer supplied by Haake.

- 25 The stated amounts of acid mean, unless indicated otherwise, percentages by weight, of concentrated HCl (37% strength), based on the amount of cellulose ether employed.

Examples 1 to 12

- 30 14 kg of water are heated to boiling in a 30 l glass vessel supplied by QVF stirred with a paddle stirrer. The appropriate amount of concentrated hydrochloric acid is then slowly added, and 5 kg (absolutely dry) of starting material are scattered in as water-moist product (dry content about 60%). After this, 50 g of H_2O_2 (100%) is

introduced as aqueous solution of any concentration through a dropping funnel, which corresponds to employing an amount of 1% by weight based on the cellulose ether.

- 5 The mixture is stirred at 90 to 100°C for the time stated in Table 1 and is then neutralized to pH 6.5 to 7.5 by slow addition of an equimolar amount of dilute sodium hydroxide solution (1 part of concentrated NaOH (50% strength) + 3 parts of water) over the course of 30 minutes.

- 10 The resulting product is filtered hot with suction through a glass frit of appropriate pore size and washed with a little boiling water in order to remove residues of suspending agent, some of which have considerable color, from the product. The product is then dried and comminuted in a commercially available mill. The grinding parameters chosen for this are such that the resulting granules have the following particle size distribution:

- | | |
|----------------------------|--------|
| > 500 μm | < 5 % |
| 15 500 – 125 μm | > 85 % |
| < 125 μm | < 10 % |

The characteristic analytical data summarized in Table 1 are determined for the granules.

- 3) basis: DIN standard 5033; measured with LF 90 colorimeter (manufactured by Dr. Bruno Lange) against white standard (enamel white standard; reflectance setting = 71.5%) by measuring the reflectance in % at a defined wavelength; UME 3 universal measuring unit, LF 90 color sensor,
- 5 measurement geometry 0°/45°, normal light type C, glass cuvette, blue filter BG12/5 (447 nm), light protection cap d = 50 mm
- 4) NaCl content due to neutralization of hydrochloric acid with sodium hydroxide solution
- 5) Transmission measured in 1.0% strength aqueous solution (absolutely dry)
- 10 at 578 nm and 415 nm against water as standard
- 6) with addition of 10 g of H₂O₂
- 7) with addition of 50 g of NaClO₂

Examples 13 and 14

15

The process is as described in Example 1 to 12 with the exception that 25 kg of water is initially present, instead of 14 kg, and 3.75 kg (absolutely dry) of moist crude product are used for the degradation.

Table 2: Acid-catalyzed degradation of hot water-coagulable cellulose ethers (MHEC) with and without additional oxidizing agent

Ex. No.	Starting material ¹⁾	HCl [% by wt]	Time [h]	H ₂ O ₂	Viscosity [mPas]	Salt [%]	Transm. [%]	
					2.0 %		578	415
13	D	16	1.0	-	8.3	0.01	94	88
14	D	16	1.0	+	7.0	0.01	96	91

- 5 ¹⁾ D Linters pulp 4, methylhydroxyethylcellulose, OCH₃ = 27.8%, OC₂H₄ = 5.1% (air-dry with 1.4% moisture content); water-moist crude product, dry content about 59%, initial viscosity before degradation (1.9%, absolutely dry): 176 000 mPas